T cell antigen discovery via trogocytosis.

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Public Summary:
A cell that is infected with a pathogen—for example, HIV—will display a bit of the invader's genetic material on the cell surface, like waving a red flag to indicate what is going on inside the cell. These "flags" are called antigens. Antigens are not limited to the marks of foreign invaders, though—they can be signatures of cancer. When a T cell finds a cell displaying its target antigen, the T cell will bind to it and destroy it. Sometimes this process can lead to autoimmune diseases if T cells begin to target healthy cells. There are one- to five million unique T cells on average in a human, encoding for as many as [approximate number] different pathogens. Though scientists can characterize the shape and molecular makeup of a T cell's receptor, it is difficult to determine what target a given receptor specifically recognizes. In fact, less than 1,000 antigen-T cell pairs are known. This method takes advantage of a natural phenomenon called trogocytosis. This occurs when a T cell and its target cell bind together and exchange proteins that are on their surfaces. It is still unclear why trogocytosis happens, but the researchers in the Baltimore laboratory decided to take advantage of the phenomenon and use it as a kind of indicator in order to determine T cell targets. To do this, the researchers made a pool of antigen presenting cells, each presenting a unique antigen and then exposed them to T cells expressing a given TCR of interest. Only the cells presenting the correct antigen will acquire markers from the T cell. Afterwards, the antigen corresponding to the T cell would then be identified by the marker on its surface.

Scientific Abstract:
T cell receptor (TCR) ligand discovery is essential for understanding and manipulating immune responses to tumors. We developed a cell-based selection platform for TCR ligand discovery that exploits a membrane transfer phenomenon called trogocytosis. We discovered that T cell membrane proteins are transferred specifically to target cells that present cognate peptide-major histocompatibility complex (MHC) molecules. Co-incubation of T cells expressing an orphan TCR with target cells collectively presenting a library of peptide-MHCs led to specific labeling of cognate target cells, enabling isolation of these target cells and sequencing of the cognate TCR ligand. We validated this method for two clinically employed TCRs and further used the platform to identify the cognate neoepitope for a subject-derived neoantigen-specific TCR. Thus, target cell trogocytosis is a robust tool for TCR ligand discovery that will be useful for studying basic tumor immunology and identifying new targets for immunotherapy.

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